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N-Protecting Group Tuning the Enantioselectivity in Strecker Reactions of Trifluoromethyl Ketimines to Synthesize Quaternary α-Trifluoromethyl Amino Nitriles by Ion Pair Catalysis

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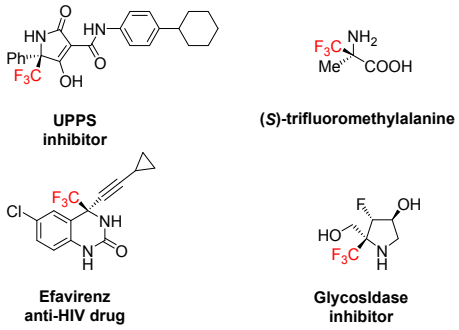
An enantioselective Strecker reaction to construct trifluoromethylated quaternary stereocenters with *N*-PMP and unexplored *N*-Boc trifluoromethyl ketimines catalyzed by organophosphine dual-reagent catalyst has been developed. The enantioselectivities of the corresponding products with the same catalyst could be switched by using different *N*-protecting group (*N*-PMP or *N*-Boc). The trifluoromethyl amino nitriles were obtained in high yield and high enantioselectivity in a short time and could be easily converted to a variety of useful trifluoromethyl-containing compounds.

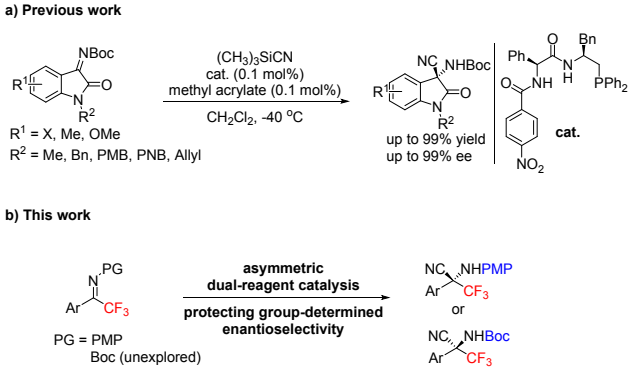
Trifluoromethyl-containing amines, amino acids and related compounds play an important role in chemical building blocks, biological compounds and drugs (Scheme 1).[1-3] The catalytic enantioselective Strecker reactions is one of the most practical and facile methods for the transformation of aldimines and ketimines into the corresponding optically active α-amino nitriles, which are easily converted into amino acids and amine derivatives.[4] In 2010, Enders and coworkers reported the first catalytic enantioselective Strecker reaction of *N*-PMP-protected trifluoromethyl ketimines for the synthesis of α-quaternary α-trifluoromethyl amino acids[5a], and later, Zhou[5b, 5e, 5g], Ma[5c], Wang[5d] and Nenajdenko[5f] reported similar reactions. They have used bifunctional Lewis base-thioureas as organocatalysts to promote the Strecker reactions with various imines. However, most of the reactions need longer time to complete.

Recently, our group has developed a novel asymmetric dual-reagent catalyst,[6,7,8] which is generated in situ by the chiral amino-acid derived organophosphine and methyl acrylate, to effectively control the Mannich reactions,[6,7] Strecker reactions,[8]



Scheme 1 Representative biologically active compounds bearing a trifluoromethylated quaternary amine motif.

Michael additions,[9a] as well as aldol reactions[9b] in high enantioselectivity. The reactions feature a low catalyst loading and high efficiency under homogeneous ion-pairing catalysis which has largely expanded the application of organophosphine catalysis. In continued efforts to explore the asymmetric organophosphine catalysis, we now wish to report protecting group (PMP or Boc)-determined enantioselective Strecker reactions of α-trifluoromethylated ketimines under ion pair catalysis (Scheme 2). To the best of our knowledge, few reports



Scheme 2 Asymmetric dual-reagent catalysis in Strecker reaction.

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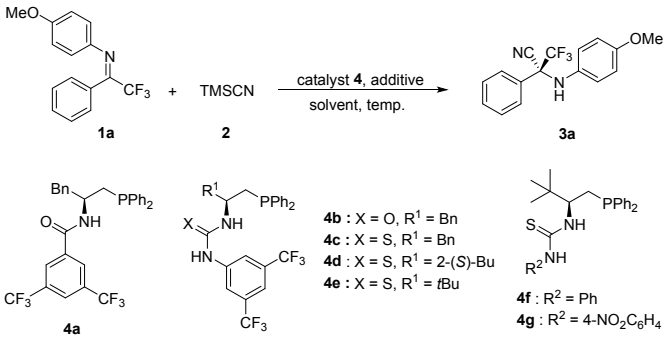
Table 1 Optimization of the reaction conditions.[a]



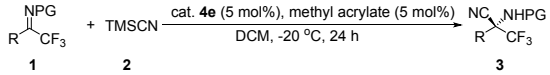
Entry	Cat.	Additive	T/h	Yield/%[b]	ee/%[c]
1	**4a**	Methyl acrylate	3	90	0.
2	**4b**	Methyl acrylate	3	88	41
3	**4c**	Methyl acrylate	3	91	60
4	**4d**	Methyl acrylate	3	85	68
5	**4e**	Methyl acrylate	3	93	85
6	**4f**	Methyl acrylate	3	91	78
7	**4g**	Methyl acrylate	3	90	82
8[d]	**4e**	Methyl acrylate	3	89	84
9[e]	**4e**	Methyl acrylate	3	87	67
10[f]	**4e**	Methyl acrylate	3	88	80
11[g]	**4e**	Methyl acrylate	7	82	84
12	**4e**	Benzyl acrylate	3	85	80
13	**4e**	*tert*-Butyl acrylate	3	82	84
14	**4e**	Methyl vinyl ketone	3	83	62
15	**4e**	Acrylamide	4	82	56
16	**4e**	N,N-Dimethyl acrylamide	4	80	83
17[h]	**4e**	Methyl acrylate	10	90	88
18[i]	**4e**	Methyl acrylate	24	89	91

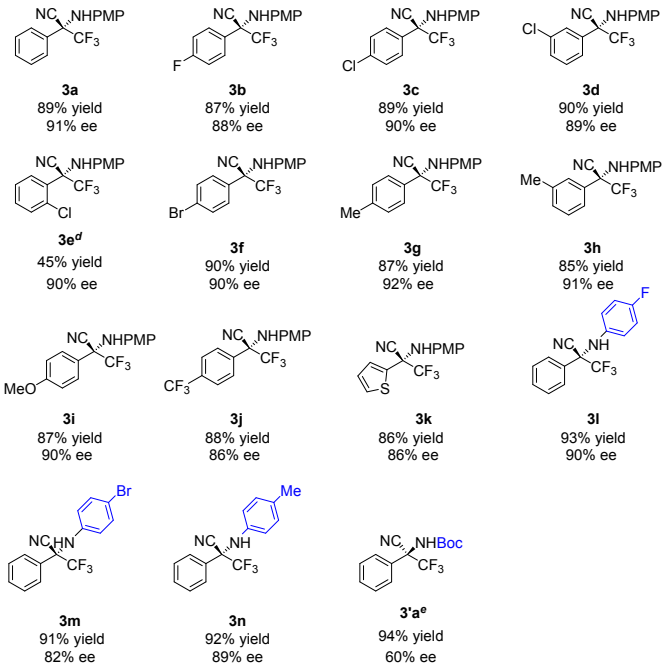
[a] Reaction conditions: 0.10 mmol **1a**, 0.20 mmol **2,** methyl acrylates (5 mol%), chiral phosphine **4** (5 mol%), DCM (1.0 mL), rt. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis. [d] $CHCl_3$ was used as the solvent. [e] Toluene was used as the solvent. [f] Et_2O was used as the solvent. [g] **4e** (1 mol %) was used. [h] Reaction was conducted at 0 °C. [i] Reaction was conducted at -20 °C.

of trifluoromethyl ketimines bearing a more cleavable *N*-Boc group[10] have been reported in Strecker reactions and other catalytic asymmetric reactions.

Initially, the commonly used *N*-PMP trifluoromethyl ketimines were tested under dual-reagent catalysis in DCM at room temperature. When the amide catalyst **4a** was employed, the product **3a** was obtained in high yield which demonstrated the ability of ion-pair catalysis[11,12] in this Strecker reactions although it was racemic (Table 1, entry 1). Then the double hydrogen-bonding catalyst **4b** and **4c** were chosen to catalyze the reaction (Table 1, entries 2-3). To our delight, improved enantioselectivity (60% ee) was observed with thiourea catalyst **4c** which implied the possible interaction between fluorine and H-bonding.[5b,13] The skeleton of the organophosphine catalysts[14] was herein investigated, which shown the catalyst **4e** from L-*tert*-Leucine was the best. Other catalysts, **4f** and **4g**, from L-*tert*-Leucine with different aryl group on thiourea moiety gave similar results (Table 1, entries 3-7). The following screening of solvents, catalyst loading, and the additives indicated the reactions were best to be performed with 5 mol% of **4e** in DCM using methyl acrylate as the additive (Table 1, entries 8-16). Lowering the temperature to -20 °C further improved the enantioselectivity to 91% ee (Table 1, entries 17-18). The absolute stereochemistry of **3a** was determined to be *R* by comparing the optical rotation with the reported value.[5a, 5b] With the optimized reaction conditions in hand, a series of *N*-PMP trifluoromethyl ketimines were investigated. It seemed that substituents on the aryl ring including the electron-withdrawing and electron-donating groups were well tolerated, giving the corresponding products in high yields with high enantioselectivities (Table 2, **3a-3j**). In addition, the heteroaromatic α-amino nitriles could also be obtained in 86% yield and 86% ee (Table 2, **3k**). Substrates with other protecting groups such as *N*-(4-fluorophenyl) imine, *N*-(4-bromophenyl) imine and *N*-(4-methylphenyl) imine also showed good results (Table 2, **3l-3n**).

Table 2 The Strecker reaction of *N*-PMP trifluoromethyl ketimines catalyzed by the dual-reagent catalysis.[a,b,c]

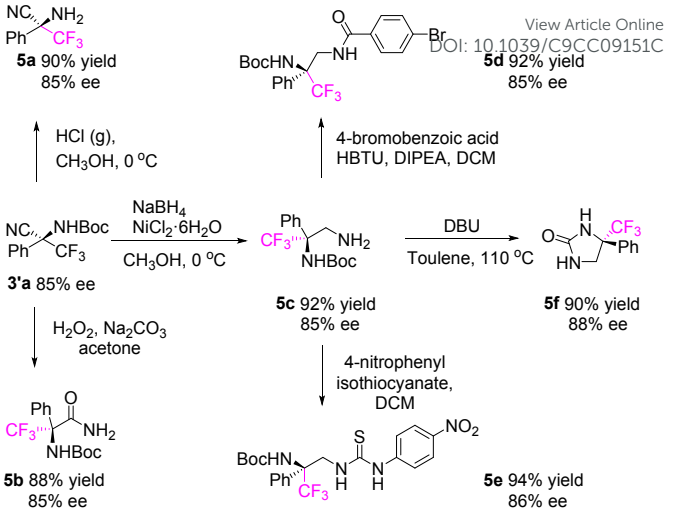




[a] Reaction conditions: **1** (0.10 mmol), 2 (0.20 mmol), methyl acrylate (5 mol%), chiral phosphine **4** (5 mol%), DCM (1.0 mL), -20 °C. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis. [d] Reaction time: 3 d. [e] Reaction time: 1 h.

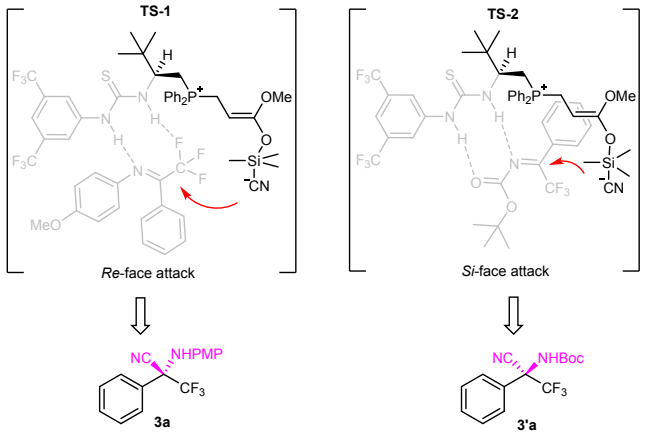
Interestingly, a tentative evaluation of the *N*-Boc trifluoromethyl ketimine gave the product with 60% ee in one hour (Table 2, **3'a**). This is very exciting since the Boc-protecting group could be removed more easily in view of the practicality of this reaction[10] and this is the first example to use *N*-Boc trifluoromethyl ketimine as the substrate in the asymmetric Strecker reaction. To improve the enantioselectivity, a few more conditions were screened (see Supporting Information for details). When the reaction was performed at -72 °C, the product could be obtained in 91% yield and 85% ee in only 2 hours, which demonstrated the superior efficiency of the dual-reagent catalysis in Strecker reactions. As shown in Table 3, this reaction was applicable to various *N*-Boc trifluoromethyl ketimines bearing electron-withdrawing substituents or electron-donating substituents on the aromatic ring, furnishing the expected products in high yields with good to high enantioselectivities. The absolute configuration of the *N*-Boc products was then determined to be *S* based on X-ray crystal structural analysis of **3'i** after recrystallization.[17] To our surprise, a switch of the enantioselectivity was observed comparing to the *N*-PMP products. In general, tunable enantioselectivity in catalytic asymmetric reactions is still very challenging especially by using a single chiral catalyst.[15] So far, limited examples have been discovered under organocatalysis to tune the enantioselectivity by varying the solvents,[16a] additives[16b] or reagents.[16c,16d] These results not only demonstrate the versatility of the organophosphine dual-reagent catalysis in controlling the enantioselectivity, but also largely expanded its application in constructing quaternary stereocenters under mild conditions.

The reaction could be conducted on gram scale without decreasing the ee. The achieved α-trifluoromethyl-α-amino nitrile **3'a** was conveniently de-protected under acidic conditions and was transformed into varieties of new compounds, such as the amide **5b** and diamine compound **5c,** in good yields (Scheme 3). The compound **5c** could be further transformed into amide **5d**, the amino-thiourea **5e** and imidazolidinone **5f** under ordinary conditions. The divergent synthesis of these derivatives provides an efficient way towards the motifs containing the trifluoromethyled amines or analogs.



Scheme 3 Transformations of the product **3'a**.

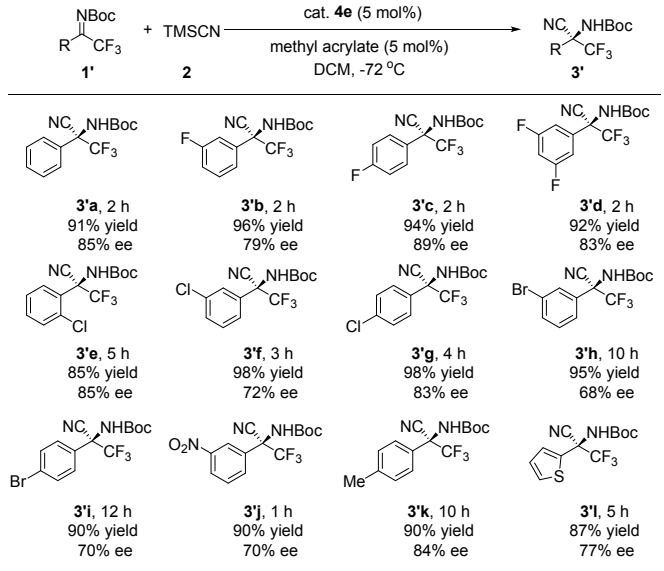
As for the enantioselectivity control and switch under the dual-reagent catalysis, we proposed the transition states of the reactions with *N*-PMP and *N*-Boc substrates as indicated in Scheme 4.[5,13] The substrate **1a** with PMP group could combine to the catalyst **4e** via the N-H and F-H bonding, while the substrate **1'a** with *N*-Boc group may interact with the catalyst **4e** via O-H and N-H bonding. The face selectivity of the complex was controlled by the steric hinderance and the C=N bond should be close to the attacking cyanide anion. Herein, the reaction in TS-1 happened via the *Re*-face and in TS-2 happened via the *Si*-face affording two products **3a** and **3'a** in opposite configuration.



Scheme 4 Proposed transition states leading to the opposite configuration.

In conclusion, we have achieved the catalytic asymmetric Strecker reaction of trifluoromethyl ketimines by organophosphine dual-reagent catalysis under mild conditions.

Table 3 The Strecker reaction of *N*-Boc trifluoromethyl ketimines catalyzed by the dual-reagent catalysis.[a,b,c]



[a] Reaction conditions: **1'** (0.10 mmol), **2** (0.20 mmol), methyl acrylate (5 mol%), chiral phosphine **4e** (5 mol%), DCM (1.0 mL), -72 °C. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis.

With the same catalyst **4e**, an enantioselectivity switch was observed when the protecting group of ketimines is changed from PMP to Boc. The reactions complete in a short time affording chiral α-trifluoromethyl-α-amino nitriles in high yields and good to excellent enantioselectivities.

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Conflicts of interest

There are no conflicts to declare.

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17 CCDC 1961106 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.